ATTACHMENT IV

Mark up copy of Claims:

Claims:

1. A pharmaceutical composition for the treatment of the risk factors of syndrome X of Reaven comprising as active ingredient a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazideor one of its analogs(as herein defined) and metformin.
2. A pharmaceutical composition comprising an additional compound.
3. A pharmaceutical composition comprising an additional compound having an additional pharmaceutical effect.
4. A pharmaceutical composition according to Claim 2 or 3 wherein the additional compound is selected among carriers, solvents and emulgamators.
5. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog of somatostatin is Octreotide.
6. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog of somatostatin is Vapreotide.
7. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog of somatostatin is Lanreotide.
8. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analogs of somatostatin are Cyclopeptide somatostatin analogues selected among :

Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]
Cyclo[N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe]
Cyclo[Pro-Ala-D-Trp-Lys-Thr-Phe]
Cyclo[Pro-Tyr-D-Trp-Lys-Thr-Phe]
Cyclo[Pro-Phe-D-Trp-Lys-ϕ-aminobutyric-Phe]
Cyclo[N-Me-Ala-Phe-D-Trp-Lys-Thr-Phe]
Cyclo[Pro-Phe-D-Trp-Lys-Val-Phe]
Cyclo[D-Ala-D-Phe-D-Trp-L-Lys-D-Thr-N-Me-D-Phe]
Cyclo[Pro-Phe-D-Trp-Lys-Thr(Bzl)] (Bzl = (a)
Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]
Cyclo[Pro-D-Phe-D-Trp-Lys-Thr(Bzl)]
Cyclo[Ahep-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Tyr-Thr-Ser] (Ahep =(b)-[SEQ ID NO 1]-
Cyclo[Ahep-Phe-D-Trp-Lys-Thr(Bzl)]
Cyclo[Ahep-Phe-D-Trp-Lys-Thr]

Cyclo[Ahep-Phe-D-Trp-Lys-Ser(Bzl)]
Cyclo[Ahex-Phe-D-Trp-Lys-Thr(Bzl)] (Ahex = (c)
Cyclo[Aoct-Phe-D-Trp-Lys-Thr(Bzl)] (Aoct = (d)
Cyclo[Ala-Cys-Phe-D-Trp-Lys-Thr-Cys]

(a) Bzl = benzyl
(b) Ahep = 7-aminoheptanoyl
(c) Ahex = 6-aminohexanoyl
(d) Aoct = 8-amino-octanoyl;

9. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thr-ol

10. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Nal-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH_2 (Nal = (1)

11. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH_2

12. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Tyr-D-Trp-Lys-Thr-Cys]-Nal-NH_2

13. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Nal-NH_2 (Abu = (2)

14. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Tyr-D-Trp-Lys-Ser-Cys]-Nal-NH_2

15. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Nal-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH_2

16. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
c(Ahep-Trp-D-Trp-Lys-Thr-Phe) (Ahep = (3)

17. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2 (Cpa = (4)

18. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2

19. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2

20. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH_2

21. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH_2

22. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Ala-Phe-D-Trp-Lys-Ala-Nal-NH_2

23. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH_2

24. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2

25. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH2

26. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are polypeptides of the formula:
X-Lys-Asn-Phe-Phe-A-Lys-Thr-Phe-Thr-Ser-Y
wherein A is L- or D-Trp,
X is H-$(Aeg)_m$-Cys- or H-$(Aeg)_m$-Ala-Gly-Cys-,
Y is -Cys-$(Aeg)_n$-OH or
X and Y taken together are a 2-aminoethyl-glycyl group in the ring position and
m and n are 0, 1, 2, provided that
m and n are at least 1,
and their cyclic disulfide derivatives.

27. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are peptides of the formula:

Bmp-Lys-X-Phe-Phe-trp-Lys-Thr-Phe-Thr-Y-Cys-OH [SEQ ID NO 2]
3 4 5 6 7 8 9 10 11 12 13 14

in which

Bmp represents the desaminocysteine radical,

X represents Asn,

trp represents D-Trp that may be substituted in the benzene ring by a halogen atom, and

Y represents the radical of an alpha-(lower alkyl)amino-(lower alkyl)-carboxylic acid having a minimum of 4 and a maximum of 8 carbon atoms, in which the two lower alkyl radicals can be connected to one another with a single C-C bond, an oxygen atom or a sulphur (II) atom.

28. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are cyclic octapeptides of the formula

Asn-Phe-Phe-Trp-Lys-Thr-Phe-Gaba(Ar) [SEQ ID NO 3]
5 6 7 8 9 10 11 12

in which

Trp represents L-Trp or D-Trp, in which the benzene ring may be substituted by a fluorine atom, and

Gaba(Ar) represents the residue of a δ-aminobutyric acid substituted by a cyclic hydrocarbyl radical Ar selected from the group consisting of cyclohexyl; phenyl optionally substituted by halogen, nitro or phenoxy; and naphthyl optionally substituted by halogen.

29. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are compounds of formula

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-R_8
-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-Cys-R_{18}-R_{19}-Phe-Phe-D
-Trp-Lys-Thr-R_{25}-R_{26}-R_{27}-R_{28}-OH wherein R_8 is

wherein the residues B, D and E have the L-configuration, and the residues in the 2- and 7-position and any residues Y_1 4) and Y_2 4) each independently have the (L)- or (D)-configuration and compounds of the following formulae

H-Cys-Phe-(D)Trp-Lys-Thr-Phe-Cys-OH

-Asn-Phe-Phe-(D)Trp-Lys-Thr-Phe-Gaba-

-MeAla-Tyr-(D)Trp-Lys-Val-Ph

NMe-Phe-His-(D)Trp-Lys-Val-Ala.

36. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analogs are Somatostatin analogs

X-Cys-D-o-Trp-E-F-Cys-Y I-[SEQ ID NO 4]

X-Cys-Lys-Asn-Phe-D-o-Trp-E-F-Phe-Thr-Ser-Cys-Y II -[SEQ ID NO 5]

I,II, X = N-terminus anchor; Y = C-terminus anchor, G-I or its alc; wherein at least I of X, Y = cationic anchor; D = Phe Tyr, 3-(p-fluorophenyl)alanine or 3 (p-chlorophenyl)alanine residue; E = Lys, Lys(R^1); R^1 = C_{1-8}(fluoro)alkyl; F = Thr, Val, Ser; G = D- or L-Thr, Phe, or 3-(2-naphthyl)alanine residue; I = OH, NH_2, NHR^1.

37. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are peptides: $RR^1NCHR^2CONHCH(CH_2SR^4)CO$-Phe-Trp-Lys-X-$NHCHR^3CH_2SR^5$.
[R = inorg. or org. acyl group, R^1 = H, alkyl, $NCHR^2CO$ moiety = I.

$Me(CH_2)_8CO$-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol I
or D-Phe (optionally ring substituted by halo, NO_2, OH, alkyl. alkoxy); Phe, Trp, (D or L) ,may be ring substituted by NO_2, NH_2, OH, alkyl, alkoxy; Lys may be α-N-methylated and Σ-N-alkylated; X = D- or L-α-amino acid residue optionally α-N-methylated; R^3 = CO_2H, CH_2OH, carbamoyl, R^4 = R^5 = H, R^4R^5

= bond]

38. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-X-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly

Cys-X^1-x^2-Phe-Phe-D-Trp-Lys-Tys-Thr-X^3-X^4-X^5-X^6-OH

39. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Leu-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-

Cys-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Tyr-Thr-Ser-Cys-OH

40. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is
c(Spacer-Phe-D-Trp-Lys-Thr)
Spacer may stand for:
a) R,S-δ-Bn-o-AMPA
b) R-α-Bn-NMe-o-AMPA
c) Phe-Pro

41. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
H_2N-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH [SEQ ID NO 6]

42. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
H_2N-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH [SEQ ID NO 7]

43. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatim analog is:
D-β-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2

44. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
Ac-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2

45. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Trp-NH_2

46. A pharmaceutical composition according to any of Claims 1 to